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Chapter 35: Endocarditis and Bacteremia

INTRODUCTION

- *Definition: Endocarditis* is an inflammation of the endocardium, the membrane lining the chambers of the heart and covering the cusps of the heart valves. *Infective endocarditis* (IE) refers to infection of the heart valves by microorganisms, primarily bacteria.
- Endocarditis is often referred to as either acute or subacute depending on the clinical presentation. Acute bacterial endocarditis is a fulminating infection and can progress to systemic inflammatory response syndrome or sepsis, potentially leading to death within days to weeks if untreated. Subacute infectious endocarditis is a more indolent infection, usually occurring in a setting of prior valvular heart disease.
- Bacteremia reflects the presence of bacteria in the bloodstream, an otherwise sterile environment, which is identified based on the detection of any true-positive blood culture.

ETIOLOGY

- Most patients with IE have risk factors, such as preexisting cardiac valve abnormalities. Many types of structural heart disease resulting in turbulence of blood flow will increase the risk for IE. Some of the most important risk factors include the following:

  ✓ Acquired valvular dysfunction (eg, rheumatic heart disease), advanced age, cardiac implantable device, chronic heart failure, congenital heart disease (CHD), diabetes mellitus, healthcare-related exposure (high risk), HIV infection, intravenous (IV) drug use, mitral valve prolapse with regurgitation, poor dentition and/or oral hygiene, presence of a prosthetic valve (highest risk), previous IE (highest risk), vascular catheters.

- Three groups of organisms cause most cases of IE: staphylococci, streptococci, and enterococci (**Table 35-1**). Staphylococci (*Staphylococcus aureus* and coagulase-negative staphylococci) are the most common cause of prosthetic valve endocarditis (PVE) within the first year after valve surgery, and *S. aureus* is common in those with a history of IV drug abuse.
- Risk factors for bacteremia include: advanced age, chronic liver disease, diabetes mellitus, end-stage renal disease on hemodialysis, functional or anatomic asplenia, HIV infection, immunosuppressive medications, indwelling prostheses (eg, vascular catheters, surgically implanted materials, and orthopedic prostheses), IV drug use, malignancies, malnutrition and hypoalbuminemia (less than 3 g/dL [30 g/L]), neutropenia, peripheral vascular disease, corticosteroids use, recent procedures (eg, urogenital surgery, prostate biopsy, endoscopic retrograde cholangiopancreatography), solid organ or stem cell transplant, trauma or loss of skin integrity, urinary retention.

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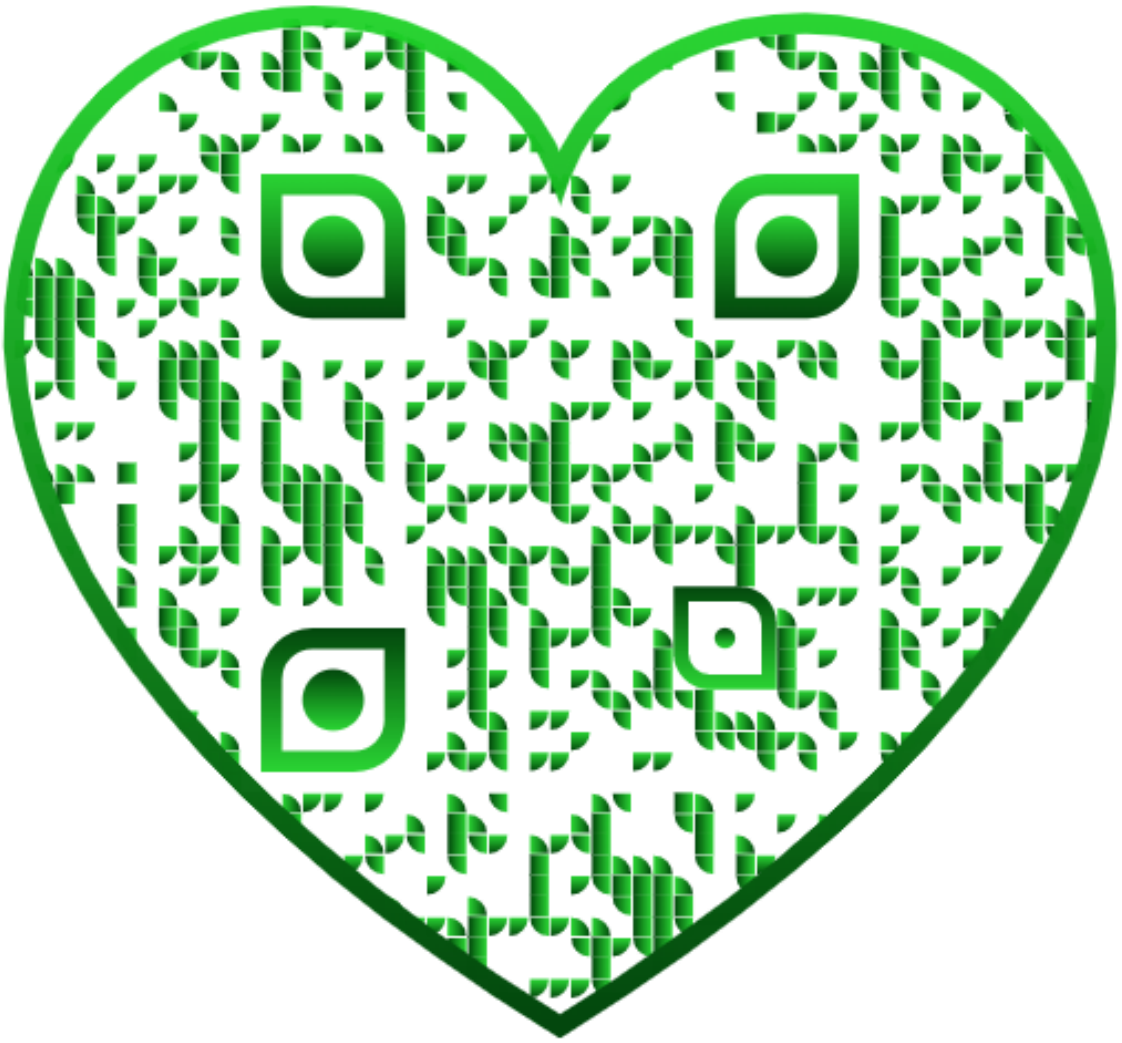

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TABLE 35-1

Etiologic Organisms in Infective Endocarditis[a]

Agent	Percentage of Cases
Staphylococcus spp.	30–70
S. aureus	20–68
Coagulase-negative (primarily *S. epidermidis* and *S. lugdunensis*)	3–26
Streptococcus spp.	9–38
Viridans group streptococci	10–28
Other streptococci	3–14
Enterococcus spp. (*E. faecalis* > *E. faecium*)	5–18
Gram-negative aerobic bacilli	1.5–13
Fungi	1–9
Miscellaneous bacteria (eg, *Coxiella burnetii*, *Bartonella* spp., *Brucella* spp.)	<5
Polymicrobial infections	1–2
Culture negative	<5–17

[a]Values encompass community-acquired, healthcare-associated, native valve, and prosthetic valve infective endocarditis.

CLINICAL PRESENTATION AND DIAGNOSIS

- The clinical presentation of patients with IE is highly variable and nonspecific. Fever is the most common finding (more than 90% of patients). The mitral and aortic valves are most often affected.
- IE usually begins insidiously and worsens gradually. Patients may present with nonspecific findings such as fever, chills, weakness, dyspnea, cough, night sweats, weight loss, or malaise.
- Important clinical signs, especially prevalent in subacute illness, may include the following peripheral manifestations (“stigmata”) of endocarditis: Osler nodes, Janeway lesions, splinter hemorrhages, petechiae, clubbing of the fingers, Roth spots, and emboli. Heart murmurs, usually preexisting, are found in most cases (approximately 85%).
- Without appropriate antimicrobial therapy and surgery, IE is usually fatal. With proper management, recovery can be expected in most patients.
- Factors associated with increased mortality include: heart failure, increasing age, endocarditis caused by resistant organisms such as gram-negative bacteria or fungi, left-sided endocarditis caused by *S. aureus*, paravalvular complications, healthcare-acquired infection, and PVE.
- The hallmark of IE is a continuous bacteremia caused by bacteria shedding from the vegetation into the bloodstream; 90%–95% of patients with IE have positive blood cultures. The patient’s white blood cell count may be normal or only slightly elevated.

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- Echocardiography plays an important role in the diagnosis and management of IE and should be performed for all patients suspected of this infection. Transesophageal echocardiography is more sensitive for detecting vegetations (90%–100%), compared with transthoracic echocardiography (40%–65%).
- The 2023 Duke-International Society for Cardiovascular Infectious Diseases (ISCVID) Infective Endocarditis Criteria, encompassing major findings of persistent bacteremia and echocardiographic findings and other minor findings, are used to categorize patients as “definite IE” or “possible IE.”
- Clinical manifestations of bacteremia vary but may involve fever, chills, rigors, altered hemodynamics, shock, coagulation disorders, cutaneous findings (eg, ulcerations), and a documented or suspected primary source of infection. Patients with bacteremia may be normothermic with a normal white blood cell count, as neither leukocytosis nor fever (≥38°C), alone or in combination, predicts the presence of bacteremia.

TREATMENT

GENERAL APPROACH

- Goals of Treatment: For IE, relieve the signs and symptoms of disease and decrease morbidity and mortality associated with infection. Eradicate the causative organism with minimal drug exposure. Provide cost-effective antimicrobial therapy. Prevent IE from occurring or recurring in high-risk patients with appropriate prophylactic antimicrobials.
- For bacteremia: Eradicate the causative organism with optimal therapy while minimizing therapeutic failure and potential for resistance; identify and manage the focal (primary) source of infection as well as any secondary foci (metastatic) of infections; relieve the signs and symptoms associated with the infection, including the bacteremia, primary source of infection, and, if present, secondary metastatic infections; decrease morbidity and mortality associated with the bacteremia and primary source of infection; and provide cost-effective antimicrobial therapy.
- The most important approach to the treatment of IE is isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by high-dose bactericidal antibiotics for an extended period.
- Treatment usually is started in the hospital, but in selected patients, it may be completed in the outpatient setting.
- Transitioning from IV to oral antimicrobials after at least 10 days of IV therapy can be used for patients with left-sided IE, a functional gastrointestinal tract, and a high likelihood of medication adherence.
- For bacteremia, empirical parenteral therapy should be based on the usual pathogens at the site(s) of presumptive primary source(s) of infection. In the case of an unknown primary source of infection or primary bacteremia (those without an obvious source), the selection of empirical parenteral antibacterial therapy should provide a broad spectrum of activity while additional diagnostic testing is performed to determine the site(s) of infection.

NONPHARMACOLOGIC THERAPY

- Surgical intervention to remove the infectious foci and repair valves and/or valvular structures is an important adjunct in the management of both native valve endocarditis (NVE) and PVE. In most cases, valvectomy and valve replacement are performed to remove infected tissues and restore hemodynamic function. Indications for surgery include heart failure, persistent bacteremia, persistent vegetation, an increase in vegetation size, or recurrent emboli despite prolonged antibiotic treatment, valve dysfunction, paravalvular extension (eg, abscess), or endocarditis caused by resistant organisms.

STREPTOCOCCAL ENDOCARDITIS

- β-Lactams remain the first-line therapy for streptococcal bacteremia. However, in patients with suspected *S. pneumoniae* bacteremia, combination empirical therapy with IV vancomycin and ceftriaxone is recommended pending susceptibility results, particularly until central nervous system involvement is excluded.

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- For the empirical management of group A streptococcal (*Streptococcus pyogenes*) bacteremia, IV penicillin (or ceftriaxone) should be combined with linezolid or IV clindamycin. Once patients achieve clinical and hemodynamic stability, typically within 48–72 hours, linezolid or clindamycin can be discontinued, particularly in those without shock, organ failure, or necrotizing fasciitis.
- In most cases of streptococcal bacteremia, monotherapy with IV penicillin or ceftriaxone is appropriate once susceptibility results are available, although oral-stepdown therapy may be appropriate for those with uncomplicated bacteremia.

STAPHYLOCOCCAL ENDOCARDITIS

- Endocarditis is most commonly caused by staphylococci, in particular *S. aureus*, mainly because of increased IV drug use, more frequent use of peripheral and central venous catheters, and increased frequency of valve replacement surgery. Coagulase-negative staphylococci (usually *S. epidermidis*) are prominent causes of PVE.
- For patients with left-sided NVE caused by methicillin-susceptible *S. aureus*, the recommended treatment is 6 weeks of nafcillin (or an alternative antistaphylococcal or penicillinase-resistant penicillin) or cefazolin. Complicated infections (like perivalvular abscess or septic metastases) may require longer durations.
- Guidelines no longer recommend the addition of gentamicin because clinical benefit has not been demonstrated and there is an increased risk of toxicity.
- If a patient has hypersensitivity to penicillin, **cefazolin** may be an effective alternative.
- **Vancomycin** is an alternative option for individuals unable to receive an antistaphylococcal or penicillinase-resistant penicillin or cefazolin, but it is less effective against *S. aureus.* Penicillin-allergic patients who fail on vancomycin therapy should be considered for penicillin desensitization or **daptomycin.**

Treatment of *Staphylococcus* Endocarditis in Persons Who Inject Drug (PWID)

- IE in PWID is most frequently (60%–70%) caused by *S. aureus*, although other organisms may be more common in certain geographic locations.
- A 2-week course of **nafcillin** (or an alternative antistaphylococcal or penicillinase-resistant penicillin), cefazolin, or daptomycin without an aminoglycoside is recommended. If vancomycin is selected, the standard 6-week regimen should therefore be used.

Treatment of Staphylococcal Prosthetic Valve Endocarditis

- PVE that occurs within 2 months of cardiac surgery is usually caused by staphylococci implanted at the time of surgery. Methicillin-resistant organisms are common. Vancomycin is the cornerstone of therapy.
- **Gentamicin** is combined with an antistaphylococcal or penicillinase-resistant penicillin or vancomycin for the first 2 weeks to enhance antistaphylococcal activity if the organism is aminoglycoside susceptible.
- For methicillin-resistant staphylococci (both methicillin-resistant *S. aureus* and coagulase-negative staphylococci), **vancomycin** is used with rifampin for 6 weeks or more.
- For methicillin-susceptible staphylococci, an antistaphylococcal or **penicillinase-resistant penicillin** is used in place of vancomycin. If an organism is identified other than staphylococci, the treatment regimen should be guided by susceptibilities and should be at least 6 weeks in duration. Rifampin should not be started until the bacterial density has decreased or blood cultures have sterilized.

ENTEROCOCCAL ENDOCARDITIS

- Enterococci are the third leading cause of endocarditis. No single antibiotic is bactericidal and there is a high relapse rate to penicillin. Combinations of a cell wall–active agent, such as penicillin or vancomycin, plus an aminoglycoside are necessary for killing.
- Enterococcal endocarditis ordinarily requires 4–6 weeks of high-dose **penicillin G** or **ampicillin** plus **gentamicin** for cure. Ampicillin plus

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ceftriaxone is as effective as ampicillin or IV penicillin G plus gentamicin. A 6-week course is recommended for patients with symptoms lasting longer than 3 months. Relatively low serum concentrations of aminoglycosides appear adequate for successful therapy, such as a gentamicin peak concentration of approximately 3–4 mcg/mL (mg/L; 6.3–8.4 µmol/L).

- β-lactamase–producing enterococci (especially *Enterococcus faecium*) are increasingly reported. If these organisms are discovered, use of vancomycin in combination with gentamicin should be considered.

EVALUATION OF THERAPEUTIC OUTCOMES

- The evaluation of patients treated for IE includes assessment of signs and symptoms, blood cultures, microbiologic tests (eg, minimum inhibitory concentration, minimum bactericidal concentration, or serum bactericidal titers), serum drug concentrations, and other tests to evaluate organ function.
- Persistence of fever beyond 1 week may indicate ineffective antimicrobial therapy, emboli, infections of intravascular catheters, or drug reactions. In some patients, fever may persist even with appropriate antimicrobial therapy.
- After initiating antimicrobial therapy, follow-up blood cultures should be obtained every 24–48 hours until sterile in most patients with gram-positive bacteremia, as the duration of bacteremia may impact the duration of therapy
- Routine follow-up blood cultures may be unnecessary except in patients who remain febrile despite antimicrobial therapy, relapse, or lack source control.
- If bacteria continue to be isolated from blood beyond the first few days of therapy, it may indicate that the antimicrobials are inactive against the pathogen or that the doses are not producing adequate concentrations at the site of infection.
- Rheumatoid factor may be used as an inflammatory marker to assess progress of the infection.

PREVENTION OF ENDOCARDITIS

- Antimicrobial prophylaxis is used to prevent IE in patients believed to be at high risk.
- The use of antimicrobials for this purpose requires consideration of the types of patients who are at risk; the procedures causing bacteremia; the organisms that are likely to cause endocarditis; and the pharmacokinetics, spectrum, cost, and ease of administration of available agents.
- IE prophylaxis should be recommended only for patients with underlying cardiac conditions associated with the highest risk, which includes the presence of a prosthetic heart valve, prosthetic material used for cardiac valve repair, prior diagnosis of IE, cardiac transplantation with subsequent valvulopathy, unrepaired cyanotic CHD or repaired CHD with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device, for dental procedures involving manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa, invasive respiratory procedures involving an incision or biopsy, or invasive procedures involving infected skin, skin structures, or musculoskeletal tissues.
- Antibiotic regimens for a dental procedure are given in **Table 35-2**.

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TABLE 35-2

Prophylaxis of Infective Endocarditis

Highest Risk Cardiac Conditions	Presence of a prosthetic heart valve Prosthetic material used for cardiac valve repair Prior diagnosis of infective endocarditis Cardiac transplantation with subsequent valvulopathy Congenital heart disease[a]	
Types of Procedures	Dental procedures that require perforation of the oral mucosa or manipulation of the periapical region of the teeth of gingival tissue Invasive respiratory procedures involving an incision or biopsy Invasive procedures involving infected skin, skin structures, or musculoskeletal tissue	
Antimicrobial Options	**Adult Doses[b]**	**Pediatric Doses[b] (mg/kg)**
Oral amoxicillin	2 g	50
IM or IV ampicillin[c]	2 g	50
IM or IV cefazolin or ceftriaxone[c,d,e]	1 g	50
Oral cephalexin[d,e,f]	2 g	50
Oral azithromycin or clarithromycin[e]	500 mg	15
Doxycycline[e]	100 mg orally	<45 kg, 2.2 mg/kg orally >45 kg, 100 mg orally
Cefazolin or ceftriaxone[e]	1 g IM or IV	50 mg/kg IM or IV

IM, intramuscular; IV, intravenous.

[a]Includes only the following: unrepaired cyanotic CHD, prophylaxis within the first 6 months of implanting prosthetic material to repair a congenital heart defect, and repaired CHD with residual defects at or adjacent to prosthetic material.

[b]All one-time doses administered 30–60 minutes prior to initiation of the procedure.

[c]For patients unable to tolerate oral medication.

[d]Should be avoided in patients with immediate-type hypersensitivity reaction to penicillin or ampicillin (eg, anaphylaxis, urticaria, or angioedema).

[e]Option for patients with nonimmediate hypersensitivity reaction to penicillin or ampicillin.

[f]May substitute with an alternative first- or second-generation cephalosporin at an equivalent dose.

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See Chapter 139, Infective Endocarditis, authored by Daniel B. Chastain, David B. Chuck, and Kelly L. Covert for a more detailed discussion of this topic.

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